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APPLICATION NUMBER:

208065Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 20, 2015
From	Gideon M. Blumenthal, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	NDA 208065
Applicant	Astra Zeneca Pharmaceuticals LP
Date of Submission	June 5, 2015
PDUFA Goal Date	February 5, 2016 (priority)
Proprietary Name / Established (USAN) names	Osimertinib (TAGRISSO)
Formulation	Tablets: 80 mg; 40mg
Dosing Regimen	80 mg by mouth once daily with or without food
Proposed Indication(s)	(b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy
Recommended:	<i>Accelerated Approval</i>

Discipline and Consultants	Primary/ Secondary Reviewer
Clinical Review	Sean Khozin, M.D., Chana Weinstock, M.D. / Gideon Blumenthal, M.D.
Statistical Review	Joyce Cheng, Ph.D./ Kun He, Ph.D.
Regulatory Project Manager	Ingrid Fan, R.P.M.
Pharm/Tox Review	Shawna Weis, Ph.D./ Whitney Helms, Ph.D.
CMC Reviews	CMC: Mike Adams Ph.D./ Olen Stephens, Ph.D. ONDS: Charles Jewell, Ph.D./ Kasturi Srinivaschar, Ph.D. Biopharm: Gerlie Gieser, Ph.D./ Okpo Eradiri, Ph.D. Micro: Ying Zhang, Ph.D. RBPM: Rabiya Laiq
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1. Introduction

On June 5, 2015, Astra Zeneca Pharmaceuticals LP (heretofore referred to as the Applicant) submitted the final component of NDA 208065 for osimertinib (Tagrisso, AZD9291) for a proposed indication of patients with [REDACTED]^{(b) (4)} metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Osimertinib is a new molecular entity (NME) pyrimidine-based irreversible EGFR kinase inhibitor that was designed to have activity against both EGFR TKI sensitivity conferring mutations such as exon 19 deletion and exon 21 substitution, as well as the gatekeeper EGFR T790M resistance mutation. Osimertinib is being studied under IND 117879, which was activated on July 11, 2013, when the first in human phase 1 study (AURA1) was allowed to proceed. Based on preliminary clinical evidence of a substantial improvement over available therapy, FDA granted osimertinib Breakthrough Therapy Designation on April 15, 2014.

The primary basis for the NDA are the results from 411 patients enrolled in D5160C00001 (AURA extension) and D5160C00002 (AURA2), two open-label, single arm trials of patients with prospectively centrally confirmed T790M mutation metastatic NSCLC who progressed on EGFR TKI. There are ongoing randomized controlled studies testing osimertinib versus platinum doublet chemotherapy (AURA3) in patients with resistant disease, and comparing osimertinib versus EGFR TKI (FLAURA) in patients with metastatic treatment naïve disease.

2. Background

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined. It is estimated that there will be 158,040 deaths due to lung cancer in 2015, comprising 27% of all cancer deaths in the U.S. NSCLC accounts for approximately 85% of lung cancer, with an expected 5-year survival of 1-5% for advanced disease.

EGFR mutation positive NSCLC accounts for about 15% of lung cancer in the United States, and 30 to 50% of lung cancer in Asia. EGFR mutations are more frequent in patients who are female, never-smokers, and have adenocarcinoma histology.

FDA approved therapies for first line treatment of patients with common EGFR mutations (exon 19 deletion and exon 21 L858R substitution mutation) include TKIs erlotinib (Tarceva; Astellas), afatinib (Gilotrif; Boehringer Ingelheim) or gefitinib (Iressa; Astra Zeneca). These TKIs are associated with Overall Response Rates (ORR) of about 60 to 70%, median Progression-Free Survival (PFS) of about 8 to 10 months, and median Overall Survival of about 24 to 30 months.

Unfortunately, resistance invariably occurs to the EGFR TKIs erlotinib, gefitinib, and afatinib. In about 50 to 60% of patients, the resistance gatekeeper T790M mutation becomes the dominant clone for patients who progress on erlotinib, gefitinib, and afatinib. There are no FDA approved therapies specifically targeting the EGFR T790M resistance mutation. (b) (4)

Other agents include single agent chemotherapy, including docetaxel and pemetrexed (associated with ORR of about 10% in unselected patients), or docetaxel with ramucirumab (associated with ORR of about 22% in unselected patients). New therapies are needed for patients with EGFR mutations who progress on EGFR TKI and develop the T790M resistance mutation.

3. Device (In vitro Diagnostic)

The Applicant partnered with Roche molecular systems to submit a contemporaneous supplement to the PMA of the cobas EGFR mutation test, a real-time PCR test for the qualitative detection of exon 19 deletions, exon 20 (T790M) substitution, and exon 21 (L858R) substitution mutations of EGFR in DNA derived from formalin-fixed paraffin-embedded (FFPET) human NSCLC tumor tissue. The cobas EGFR mutation test is FDA approved to identify patients with EGFR exon 19 deletion and exon 21 (L858R) substitution mutations for whom erlotinib is indicated. The current PMA supplement is to detect EGFR exon 20 (T790M) substitution mutation positive NSCLC for whom osimertinib is indicated. Preliminary assessments include comparison of version 1 versus version 2 of the cobas tests, as well as comparison of cobas EGFR version 2 versus Next Generation Sequencing. Finalization of the CDRH review is pending, but per personal correspondence with Dr Bijwaard, the sPMA is on track to be approved contemporaneously with NDA approval.

4. CMC

- **Drug Substance:** Osimertinib mesylate is the drug substance. (b) (4)

(b) (4)

The drug substance is produced by a process using (b) (4)

(b) (4)

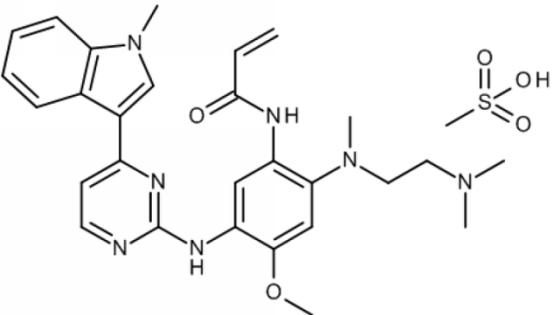
Ultimately, four impurities are specified in the

drug substance, and additionally one mutagenic impurity is specified. For this drug substance in this application the Agency is accepting a threshold of toxicological concern (TTC) for mutagenic impurities of (b) (4) ppm, based in part on ICH S9 and the dosing schedule for this product. The manufacturing process has demonstrated the ability to limit potential mutagenic impurities to below (b) (4) % of the TTC in all cases, so only the most prevalent mutagenic impurity is specified. (b) (4) is the only solvent specified. Water content in all development and commercial batches is below (b) (4) %, so microbial testing is not necessary for this drug substance on release, though microbial growth is monitored in stability testing. The drug substance is stable for (b) (4) months at long term storage and (b) (4) months under accelerated storage. This reduced stability set was accepted based on accelerated development of this breakthrough designated product and not actual stability demonstration. Supportive stability data supports a re-test period of around (b) (4) months when stored in double wrapped (b) (4) (b) (4) stored in rigid outer containers at (b) (4).

The Applicant proposed a comparability protocol to change the (b) (4)

The proposed protocol would report this change as a CBE (0). Table 1 provides a description of the chemical properties of osimertinib.

Table 1: Chemical properties of osimertinib

	<ul style="list-style-type: none">• AZD9291 mesylate• $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$• MW: (b) (4) (mesylate salt)• MW: (b) (4) (free base)• CAS registry #: 1421373-66-1• (b) (4)• (b) (4)• pKa: 9.5 and 4.4• (b) (4)• melting onset: 248°C (DSC)• (b) (4)
IUPAC Name:	(b) (4)

- **Drug Product:** Tagrisso is osimertinib mesylate formulated as 40 mg or 80 mg free base (equivalent to 47.7 and 95.4 mg mesylate, respectively) film-coated tablets (b) (4). The 40mg tablet is 9mm round, biconvex, beige and debossed with 'AZ' over '40' on one side and plain on the reverse. The 80mg tablet is 7.25x14.5mm oval, biconvex, beige and debossed with 'AZ 80' on one side and plain on the reverse. The tablet core is composed of mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. Both tablets use the same film-coating which is composed of polyvinyl alcohol, titanium dioxide,

(b) (4) 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

The bulk tablets are manufactured in (b) (4). The bulk tablets are (b) (4) tablets. The package for bulk (b) (4) composed of (b) (4) (b) (4). Bulk tablet are to be stored at (b) (4). The finished package for both tablet strengths is a 30-count HDPE bottle with (b) (4) screw cap, (b) (4).

The controls and specification for excipients, the manufacturing process, bulk tablets and finished product are described in sufficient detail. The tests and criteria in the regulatory specification are justified. The analytical methods are described in sufficient detail and validated appropriately. The protocol for post approval stability studies is acceptable. The recommended initial expiry period is 12 months in the finished package when stored at USP controlled temperature (20 °C to 25 °C (68 °F to 77 °F)). Tablets are not sensitive to light (b) (4).

(b) (4) has been used throughout the development of AZD 9291 film-coated tablets. (b) (4)

The overall manufacturing process has been studied and optimized for risks posed by (b) (4)

For each unit operation, the applicant identified the failure mode and related quality attributes of drug product.

For drug product, the Applicant did not include the microbial control in the release specifications. They included microbial control (TAMC, TYMC and absence of *E. Coli.*) in the primary stability studies under long-term conditions, and stated such control will be monitored annually until the end of these studies.

Overall, debossing did not negatively impact the complete release of osimertinib from the 40 mg tablets and the 80 mg tablet cores used in the AURA extension and AURA2. The Applicant proposes not to use disintegration in lieu of dissolution testing as a routine QC test since there was no observed correlation between dissolution and disintegration rates of osimertinib tablets. Furthermore, there was no observed link between tablet core hardness and disintegration time.

The proposed dissolution method exhibits discriminating capability as it was able to detect differences in (b) (4) to and/or tablet hardness of different clinical batches of 40 mg tablets. The apparent limited influence of

manufacturing and formulation variables on the dissolution profiles of osimertinib tablets could be explained at least in part by the high solubility of the drug substance over a wide pH range. The proposed dissolution method is adequate to assure batch-to-batch variability via monitoring complete dissolution of osimertinib tablets at the time of manufacturing release and during stability testing.

Judging from the findings of the relative BA study (Study 5), the oral bioavailability of osimertinib is not expected to be negatively impacted when administered as an aqueous dispersion of the tablet either orally or via a nasogastric tube, because the oral bioavailability of the intact oral tablet is comparable to that of the oral solution. Some lung cancer patients who had developed difficulty swallowing tablets received osimertinib as a pre-dispersed tablet in the clinical studies conducted. Chemical stability of an aqueous dispersion was reported to be acceptable over (b) (4), and the transfer of dispersed tablets through nasogastric tubes was shown to be suitable for administration using appropriate commercially available tubes. (b) (4)

(b) (4). However, use of heat or ultrasonication to prepare the dispersion was not compatible with this formulation and this information has been captured in the package insert.

Both 40 mg and 80 mg strengths of the proposed commercial osimertinib *debossed* film coated tablets have comparable *in vitro* dissolution characteristics [and thus are not expected to behave differently (in terms of efficacy)] to the *non-debossed* film-coated tablets evaluated in the pivotal Phase 2 clinical Studies AURA Extension and AURA2. There is adequate bridging between the clinical research and the proposed commercial formulations of osimertinib tablets.

The Applicant requested to use clinical lots formulated with lots of API campaign 4 for commercial launch drug product. The Applicant confirmed that the campaign 4 drug substance batches intended to be used for launch was manufactured at the (b) (4) as listed on 356h. All batches met the proposed commercial specification, including debossing design. There is no additional risk for distributing the clinical lots manufactured at the same proposed API site as the product met all proposed commercial specification.

An overall “approval” recommendation has been rendered by the Office of Pharmaceutical Quality. There are no pending review issues and the manufacturing and testing facilities received an overall “acceptable” evaluation from the Office of Process and Facilities (04-Oct-15). An initial shelf life of 12 months in the finished package is granted when stored at USP controlled temperature (20 °C to 25 °C (68 °F to 77 °F)).

- Biopharmaceutics Considerations- BCS Classification
 - *Drug Substance*: Osimertinib exhibits high solubility and higher than moderate permeability (based on Caco-2 system and human radiolabelled

ADME Study 11), (b) (4)

In the ADME study using 20 mg oral solution, ~80% of the radioactivity was associated with metabolites and other by-products in feces and urine, and an additional 2% was attributed to the unchanged drug.

- *Drug Product*: Osimertinib tablets are very rapidly dissolving (on average, \geq (b) (4) % dissolved in (b) (4) minutes).

- **Per CMC Executive Summary from Dr. Olen Stephens, Acting Branch 2 Chief, ONDP emailed October 16, 2015**: The Office of Pharmaceutical Quality recommends NDA 208-065 for “approval” as there are no pending review or inspection issues. The manufacturing and testing facilities received an overall “acceptable” evaluation from the Office of Process and Facilities (04-Oct-15). An initial shelf life of 12 months in the finished package is granted when stored at USP controlled temperature (20 °C to 25 °C (68 °F to 77 °F)). The applicant proposed a comparability protocol to change the (b) (4)
The approval letter should include the following language, “The comparability protocol to change (b) (4) is acceptable, but this change must be reported as a CBE30 and not a CBE0.”

5. Nonclinical Pharmacology/Toxicology

- **Non clinical Pharmacology**: Osimertinib exhibited greater anti-tumor activity in murine tumor models that are predominantly driven by mutant EGFR isoforms, including T790M, L858R, or exon 19 deletion mutants, than in those that express wild-type EGFR, a finding that correlated with the increased biochemical activity of osimertinib against EGFR mutants relative to wild type EGFR. In vitro, osimertinib also exhibited the potential to inhibit other members of the EGFR family (HER2, HER3, and HER4) as well as ACK1 and BLK at clinically relevant concentrations. While some potential for inhibition of cardiac ion channels, including hERG, and the L-type calcium channels, was observed, data from the in vivo cardiovascular safety pharmacology study did not suggest notable electrocardiology effects at tolerable doses, though equivocal findings of decreased contractility occurred in dogs and guinea pigs.
- **Repeat dose toxicology**: AZD9291 was evaluated in 13-week repeat-dose toxicology studies in the rat and the dog. Consistent with its pharmacologic mechanism of action, administration of AZD9291 to dogs and rats was associated with adverse gastrointestinal (GI) clinical symptoms (loose feces, and/or inappetence), skin lesions (ulceration), and ocular lesions (corneal atrophy). Other histological target organs included the lungs (rats and dogs; macrophage infiltration) and kidney (rat). In the dog, ocular lesions were dose-limiting, whereas in the rat, GI effects were dose limiting.

The highest doses of osimertinib administered to rats in the 13-week toxicology studies produced plasma exposures that were similar to the clinical C_{max} of 501 nM and AUC of 11258 nM*h at the recommended dose of 80 mg daily. Plasma AUCs achieved in the dog study at the highest-tolerated dose of 6 mg/kg/day were approximately 0.48X those observed in patients who received the 80 mg daily oral dose.

Two major pharmacologically-active metabolites were identified in humans and animals: AZ13575104 (AZ5104) and AZ13597550 (AZ7550). The Applicant demonstrated that both metabolites exhibit comparable pharmacodynamic and target-inhibitory activities as osimertinib. In humans, plasma exposure to each metabolite is approximately 10% of those of osimertinib on the basis of both AUC and C_{max} . While exposure to both metabolites was demonstrated in the rat and the dog, the Applicant only calculated TK parameters for AZ7550 due to problems with bioanalytical reproducibility for AZ5104. In the rat, exposure to AZ7550 was approximately 0.8X those observed in humans on an AUC basis. In the dog, exposure to AZ7550 was approximately 0.51X that of humans on an AUC basis. Due to difficulties with the detection assay for AZ5104 in animals, the Applicant performed an additional 1-month metabolite-characterization study of AZ5104 in the rat. This study revealed no new toxicities at doses that exceeded the clinical exposure of this metabolite in patients treated with osimertinib. Thus, the Applicant has adequately characterized the toxicity of osimertinib and its two major metabolites.

- **Mutagenicity:** Osimertinib was non-mutagenic in bacterial and mammalian cell assays when tested in the presence and absence of metabolic activation by Aroclor-induced rat S9 liver fractions. Osimertinib was also negative for induction of structural chromosome aberrations in primary human peripheral blood mononuclear cells both in the presence and absence of metabolic activation by Aroclor-induced rat S9 liver fractions and the in vivo rat micronucleus assay.
- **Reproductive toxicity:** In an assessment of male fertility that was conducted in the context of the 13 week rat study, males were treated with osimertinib for 65 days prior to mating with untreated females. Osimertinib treatment was associated with decreases in male fertility, as demonstrated by decreased numbers of live fetal implants. These reductions were primarily due to increases in pre-implantation loss in naïve females crossed with males treated at the high dose level of 20 mg/kg and occurred at osimertinib exposures of approximately 0.5X those observed in humans at the recommended dose of 80 mg. While the mechanism for this apparent effect on male fertility has not been fully elucidated, a recommendation for male contraception for at least 4 months during treatment with TAGRISSO is warranted.

The Applicant conducted a GLP-compliant dose range-finding study of AZD9291 in pregnant dams. When administered to dams between gestation days (GDs) 2-20 (i.e. prior to implantation through the end of organogenesis), osimertinib exposure led to increased post-implantation loss and early embryonic death. The adverse effects on reproduction occurred at maternal exposures of approximately 1.5-times the clinical

C_{max} observed in patients who receive the 80 mg oral dose. No clear adverse effects on pregnancy maintenance were noted when osimertinib was administered between GD6 and GD20 at doses up to 30 mg/kg; however, an equivocal increase in the rate of fetal malformations (anencephaly and missing lung lobe) and variations was observed in treated litters relative to those of concurrent controls at doses greater than or equal to 1 mg/kg (approximately 0.1 times the AUC in patients at the 80 mg dose). Given the small number of dams included in the study and the mechanism of action of osimertinib, the relationship of these findings to osimertinib treatment cannot be excluded. When osimertinib was administered to pregnant dams during organogenesis through lactation day 6 (GDs 6-LD6), an increase in total litter loss including in postnatal death occurred at 30 mg/kg/Day. At 20 mg/kg, there was an increase in postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation Days 4 and 6. Toxicokinetic exposures were also measured in fetuses and/or nursing pups. Fetal exposure to osimertinib at the end of gestation (GD20) was approximately 36% of that observed in dams on GD16. Fetal exposure to AZ7550 was also demonstrated; however, fetal metabolite levels were relatively low - less than 7% of maternal levels. A low level of exposure to osimertinib and its metabolite was demonstrated in nursing pups, suggesting that osimertinib and/or AZ7550 may be excreted in milk. At the maternal C_{max} (2 hours post-dose), neonatal exposure to osimertinib was approximately 2% of the maternal exposure levels. Peak neonatal exposure to AZ7550, however, was approximately 12% of maternal levels at 2 hours post-maternal-dose.

Overall Recommendation [Shawna L Weis, Ph.D. and Whitney S. Helms, Ph.D., 10/8/15]: From a nonclinical perspective, TAGRISSO is approvable for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

6. Clinical Pharmacology

- **Dose Selection:** In AURA1, no DLTs were reported in the dose escalation part of the study across doses of osimertinib 20 mg to 240 mg. A formal non-tolerated dose was not determined for osimertinib. The AURA1 scientific review committee decided that based on the high activity observed across doses and increased dose modifications and frequency of EGFR wild-type events at higher doses, no further dose escalation was required. The recommended Phase 2 dose was determined to be 80 mg daily with or without food. The basis for this was the high, durable and deep responses at this dose, with doses of 160 mg and higher unlikely to provide additional benefit and likely to provide greater toxicity.
- **Pharmacokinetics:** The pharmacokinetics (PK) of osimertinib have been characterized following single dosing in healthy volunteers and in patients with advanced NSCLC following single and multiple dosing. The PK properties of osimertinib were dose and time independent across the 20-240 mg dose range. The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C_{max}) of

osimertinib increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) and exhibited linear PK.

Administration of osimertinib daily resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. The ratio of C_{max} to C_{min} (minimal concentration) was 1.6 at steady-state.

Absorption: In cancer patients, the median time to C_{max} (T_{max}) of osimertinib was 6 (range: 3-24) hours. The C_{max} and AUC of osimertinib increased by 14% and 19%, respectively, following administration of a 20 mg Phase 1 tablets with a high-fat, high-calorie meal compared to fasting conditions. (b) (4)

and these results will be submitted at a later date. No bioequivalence (BE) studies were conducted because the commercial film-coated tablet formulation was used in the Phase 2 registration trials.

Distribution: The mean volume of distribution at steady-state (V_{ss}/F) of osimertinib was 986 L. Plasma protein binding could not be measured due to instability. However, the plasma protein binding of osimertinib is likely high based on its physicochemical properties.

Metabolism: The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral osimertinib dosing. AZ7550 showed a similar potency to osimertinib, while AZ5104 showed greater against the exon 19 deletion and T790M mutants (approximately 8-fold) and wild-type (approximately 15-fold) EGFR. The geometric mean exposure (AUC) of each metabolites was approximately 10% of the exposure of osimertinib at steady-state.

Elimination and Excretion: In a mass balance study after administration of single 20 mg oral solution dose of [^{14}C]-osimertinib, 67.8% and 14.2% of radioactivities were recovered in feces and urine over 84 days, respectively. Unchanged osimertinib accounted for approximately 2% of the elimination. Osimertinib plasma concentrations decreased with time and a population estimated mean half-life was 48 hours and oral CL/F was 14.2 (L/h).

- **Drug-Drug Interaction:** Osimertinib is predominantly metabolized via CYP3A. Drug interaction studies have not been conducted. In the absence of any clinical drug- drug interactions (DDI) data, (b) (4)

Therefore, dosage recommendations in product labeling were based on information that osimertinib is a CYP3A substrate in vitro.

In vitro data indicate that osimertinib is likely to be a perpetrator of DDI through inhibition of CYP3A and breast cancer resistance protein (BCRP) transporter and

induction of CYP3A4, CYP2C, P-glycoprotein (P-gp) and CYP1A2 enzymes. Based on in vitro studies, osimertinib is a substrate of P-gp and BCRP and is not a substrate of OATP1B1 and OATP1B3 in vitro. Osimertinib is a competitive inhibitor of CYP 3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2D6 and 2E1 in vitro. Osimertinib induced CYP3A4 (Pregnane X dependent) and CYP1A2 enzymes. Osimertinib is an inhibitor of BCRP and does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 in vitro.

- **Gastric Acid Reducing Agents:** The exposure of osimertinib was not affected by concurrent administration of a single 80 mg osimertinib dose following 40 mg omeprazole administration for 5 days.
- **PK in Specific Populations:**
Renal Impairment: No dedicated clinical study has been conducted to evaluate the effect of renal impairment on the PK of osimertinib. Based on population PK (PopPK) analysis, no dose adjustment is recommended in patients with mild [creatinine clearance (CL_{cr}) 60 - 89 mL/min], and moderate (CL_{cr} 30- 59 mL/min) renal impairment. As patients with CL_{cr} less than 15 mL/min or end-stage-renal disease with or without hemodialysis were not included in the clinical trials, the appropriate dose of osimertinib is unclear in patients with severe renal impairment (CL_{cr} < 30 mL/min) or end-stage-renal disease.

Hepatic Impairment: No dedicated clinical study has been conducted to evaluate the effect of hepatic impairment on the PK of osimertinib. Based on PopPK analysis, no dose adjustment is recommended in patients with mild hepatic impairment (NCI organ dysfunction working group criteria: total bilirubin < upper limit of normal [ULN] and Aspartate aminotransferase [AST] between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 x ULN and any AST). The appropriate dose has not been determined in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.

No dose adjustment for age, sex, body weight, race or smoking status is recommended based on the results of a PopPK analysis.

- **Exposure-Response (E-R) Relationship:** A logistic regression model was used to assess the relationship between osimertinib exposure (AUC_{ss}) and efficacy/safety endpoints using data from the patient studies AURA Phase 1, AURA extension, and AURA2. There was no evidence of a relationship between exposure and probability of response. The probability of patient experiencing rash and diarrhea (all grades) increased with osimertinib exposure. However, the incidence of experiencing grade 3 or higher rash or diarrhea was less than 1%. The relationship between AZD9291 exposure and occurrence of interstitial lung disease (ILD) or ILD-like events was inconclusive.
- **QT/QTc:** A large change in QTc (i.e., >20 ms) was not detected in AURA2 following single dose or multiple doses of osimertinib. Significant QT prolongation at steady-state was observed with the maximum mean change from baseline (with the upper bound of the two-sided 90% CI) in QTcF of 16.2 (17.6) ms. A pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested a concentration-dependent QTc interval prolongation at 80 mg of 14 ms with an upper bound of 16ms (90% CI). This

drug is highly unlikely to be a hERG blocker, and, at least over the concentration range observed, would suggest there will be no further interference with repolarization at high exposure. Its modest effect likely conveys some incremental risk, although only in conjunction with other repolarization blockers, particularly real hERG blockers.

Overall Recommendation from Clinical Pharmacology (10/8/2015): This NDA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends granting approval of this NDA.

7. Clinical Microbiology

The application did not include clinical microbiology information.

8. Clinical/Statistical- Efficacy

I agree with the conclusions of the clinical efficacy (Dr. Sean Khozin) and statistical (Dr. Joyce Chen) reviewer assessments.

The following summarizes the key milestones in the regulatory history:

- July 11, 2013: The first in human phase 1 study (D5160C00001 AURA) was allowed to proceed under IND 117879.
- January 14, 2014. Type C meeting to discuss the overall NSCLC clinical development program for osimertinib to support initial registration as a treatment for relapsed, T790M positive NSCLC patients. FDA stated general agreement with AstraZeneca's proposal to conduct the confirmatory randomized trial with osimertinib versus standard platinum-based doublet chemotherapy in chemotherapy-naïve patients with acquired resistance to EGFR TKIs and T790M resistance mutations (AURA3). However, FDA highlighted that for any randomized trial, the condition of equipoise must exist.
- April 16, 2014: An application for Breakthrough Therapy Designation was granted for the treatment of patients with metastatic EGFR T790M mutation positive NSCLC whose tumor has progressed on treatment EGFR tyrosine kinase inhibitor.
- October 2, 2014: Type B Breakthrough Therapy-Initial Comprehensive meeting. The primary purpose of the meeting was to discuss and reach agreement on the development program to provide an adequate data package to support an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) for osimertinib for the treatment of patients with (b) (4)/metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy (b) (4). FDA generally agreed that demonstration of blinded independent central review (BICR) confirmed durable responses in a substantial

proportion of the second-line patients treated with osimertinib 80 mg once daily in the Phase 1 portion of D5160C00001 AURA (n~50) could potentially enable an adequate assessment of the durability of the confirmed objective responses for the purpose of making a regulatory decision. FDA generally agreed with AstraZeneca's pooling strategy for Studies D5160C00001 (AURA extension) and D5160C00002 (AURA2) in the summaries of safety and efficacy.

- October 7, 2014. Type B CMC meeting.
- December 9, 2014. Type B pre-NDA meeting. FDA agreed with AstraZeneca's approach for rolling submission. The meeting included a synopsis of the confirmatory trial, Study D5160C00007 (FLAURA), a double-blind, randomized study in patients with locally advanced or metastatic EGFR mutation-positive (EGFRm+) NSCLC who are treatment-naïve and eligible for first-line treatment with an EGFR TKI. AstraZeneca stated that the cobas® EGFR Mutation test used to identify patients' EGFR mutation status for the AURA and FLAURA studies is an investigational assay and that the test is identical to the FDA-approved cobas® EGFR Mutation test except it identifies additional EGFR mutations (e.g., T790M) that are not described in the FDA-approved labeling for this test.

Efficacy Summary:

The efficacy population was assessed in two multicenter, single-arm, open-label clinical trials, AURA extension (N=201) and AURA 2 (N=210) in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. All patients received osimertinib 80 mg once daily. The major efficacy outcome in these trials was ORR according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Duration of response (DOR) was an additional outcome measure.

AURA extension study characteristics were: median age 62 years (range 37 to 89), female (66%), White (40%), Asian (58%), never smoker (67%), Performance status 0 (34%) or 1 (66%), and number of prior therapies 3 or more (45%). Concurrent EGFR mutation distribution was Exon 19 deletion (71%), Exon 21 L858R (25%), G719X (2%), and S768I (2%).

AURA2 study characteristics were: median age 64 years (range 35 to 88), female (70%), White (34%), Asian (63%), never smoker (76%), Performance status 0 (40%) or 1 (60%), and number of prior therapies 3 or more (46%). Concurrent EGFR mutation distribution was Exon 19 deletion (65%), Exon 21 L858R (32%), G719X (2%), and S768I (1%).

Table 2 summarizes the critical features of the studies submitted to support safety and efficacy.

Table 2: Key Clinical Trials in support of the proposed indication (Source: Clinical Review page 19)

	AURA extension	AURA2	AURA Phase 1
No. of patients	201	210	355
Study No.	D5160C00001 (“P2” extension)	D5160C00002	D5160C00001 (Phase 1)
Type	Open-label, single arm trial extension of AURA phase 1 to investigate activity of osimertinib in previously EGFR TKI treated patients with metastatic EGFRm+ T790M+ NSCLC	Open-label, single-arm trial, similar population as in AURA extension	Open-label, single arm, multi-dose cohort trial with ascending doses of osimertinib in patients with advanced NSCLC who have progressed following prior therapy with an EGFR TKI agent
Key objectives	<u>Primary:</u> To investigate safety, tolerability, efficacy (ORR) <u>Secondary, extension cohort:</u> To obtain additional assessments of the anti-tumour activity of osimertinib by evaluation of DOR	<u>Primary:</u> Assess the efficacy of osimertinib by ORR. <u>Secondary:</u> To further assess the efficacy of osimertinib in terms of DOR To assess the safety and tolerability profile of osimertinib	<u>Primary:</u> To investigate safety, tolerability, efficacy (ORR) <u>Secondary, dose-escalation and dose-expansion cohorts:</u> To obtain a preliminary assessment of the anti-tumour activity of osimertinib by evaluation of DOR
T790M central testing	Performed prospectively; central result (cobas® EGFR mutation test) mandatory to determine eligibility	Performed prospectively; central result (cobas® EGFR mutation test) mandatory to determine eligibility	Performed retrospectively (cobas® EGFR mutation test)
Study period	First patient dosed: 14 May 2014 Last patient first dose: 21 October 2014	First patient dosed: 13 June 2014 Last patient first dose: 27 October 2014	First patient dosed: 6 March 2013 (80 mg subset in dose expansion: 2 September 2013) Last patient first dose: 12 November 2014 (80 mg subset: 12 November 2014)
Data cut-off (DOC)	9 January 2015	9 January 2015	2 December 2014
Treatment exposure at DCO, median and range	Median (range): 4.9 months (0.1 to 7.9 months)	Median (range): 4.0 months (0.0 to 6.9 months)	Pre-treated T790M mutation-positive in dose expansion (n = 163): Median (range): 8.7 months (0.1 to 17.7 months) 80 mg pre-treated T790M mutation-positive (n = 63): Median (range): 8.1 months (0.5 to 14.3 months)

Table 3 summarizes ORR and DOR in the key studies, including the median duration response in the 63 patients from AURA Phase 1 who had longer follow-up than in AURA extension and AURA2.

Table 3: ORR and DOR in AURA phase 1, AURA extension, and AURA 2 per BICR assessment (Source: Clinical Review page 44)

	AURA Phase 1 (n = 63)	AURA extension (n = 201)	AURA2 (n = 210)	Combined (AURA extension and AURA2) (n=411)
ORR (95% CI)	50.8% (37.9%, 63.6%)	57.2% (50.1%, 64.2%)	61.0% (54.0%, 67.6%)	59.1% (54.2%, 63.9%)
CR	0	0	2 (1.0%)	2 (0.5%)
PR	32 (50.8%)	115 (57.2%)	126 (60.0%)	241 (58.6%)
Ongoing*, n	22	113	120	233
Median DOR, months	12.4 (8.3, NC)	Not Reached	Not Reached	Not Reached

*Patients with ongoing responses as of data cut-off date
 DOR, duration of response; ORR, overall (objective) response rate
 FDA analysis

Primary Reviewers Conclusions:

I concur with Drs. Khozin and Cheng that the ORR and durability data from AURA extension and AURA2, supported by the durability from AURA Phase 1 appear to be robust and are of large magnitude and duration to reasonably predict clinical benefit for osimertinib over available therapies.

9. Safety

I concur with the safety clinical reviewer’s (Dr. Chana Weinstock’s) conclusions regarding the safety of osimertinib.

Safety Summary

The safety database was assessed based on the pooled analysis of 411 patients with metastatic EGFR T790M mutation-positive NSCLC who received prior EGFR TKI therapy in AURA extension and AURA2 who received osimertinib 80 mg daily. Of the 411 patients, 81% were exposed to osimertinib for 6 months or more; no patients were exposed for 12 months.

- Most common adverse reaction (all grades) > 20% were rash (42%), diarrhea (42%), dry skin (35%), and nail toxicity (26%).
- Most common laboratory shifts (all grades) >30% were thrombocytopenia (54%), anemia (44%), and neutropenia (33%)

- Dose reductions were infrequent, occurring in 4.4% of patients
- Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients. The most frequent adverse reactions leading to discontinuation were ILD/pneumonitis (1.9%) and cerebrovascular accidents (1%).
- The most frequent adverse reactions leading to dose reductions or interruptions were: QT prolongation (2.2%) and neutropenia (1.9%)
- Serious adverse events (SAEs) occurred in 13% of patients, the most common non-fatal SAEs include pneumonia (1.2%), pulmonary embolism (1.2%), and pneumonitis (0.7%)
- Fatal adverse events occurred in 2.5% of patients, including ILD/pneumonitis (1%, n=4), pneumonia (1%, n=4), and CVA/cerebral hemorrhage (0.5%, n=2)
- Interstitial Lung Disease: occurred in 2.7% (n=11) of patients, and was fatal in 1% (n=4)
- QT interval prolongation: 1/411 patients (<1%) had QTc greater than 500 msec, and 10 patients (2.4%) had QTc increase from baseline greater than 60 msec. No episodes of torsades or fatal arrhythmia.

Overall Safety Assessment: I concur with Dr Weinstock that the overall safety profile of osimertinib is acceptable relative to the benefits.

10. Advisory Committee Meeting

There was no advisory committee meeting for osimertinib because the safety profile is acceptable for the treatment of patients with EGFR T790M positive metastatic NSCLC who have progressed on EGFR TKI, the application did not raise significant public health questions on the role of osimertinib for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from an advisory committee discussion.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.
- **Financial Disclosures:** No issues.
- **Other GCP Issues:** None
- **Pediatrics:** Osimertinib is exempt from the pediatric study requirements of the Pediatric Research Equity Act in accordance with the provisions of 21 CFR 314.55.

Osimertinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) on September 4, 2014.

- **Office of Scientific Investigation (OSI) Audits:** Two clinical sites were chosen for inspection: Site 7800 (Dr. Pasi Janne, Boston, MA) for Study D5160C0001C (Phase II Extension Study) and Site 7401 (Dr. Chung-Ming Tsai, Taipei, Taiwan) for Study D5160C00002. These sites were selected for inspection using CDER's Clinical Site Selection Tool (CSST). The CSST uses site specific data (e.g., enrollment, AE reporting, protocol violations, inspectional history) in a multi-attribute risk prioritization algorithm to display site level data for review, and use by the application review team to select clinical investigator sites for inspection. The sponsor and one study CRO (IRC Vendor), (b) (4) were also inspected.

Overall Recommendation from Office of Scientific Investigations (10/6/2015): Tumor response data from the ICR was used to derive the primary efficacy endpoint variable of ORR for all subjects in Study D5160C0001C (Phase II Extension Study) and Study D5160C00002. The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There were no trends in underreporting adverse events.

Based on the review of preliminary inspectional findings for clinical investigators Dr. Pasi Janne (Site 7800: Study D5160C0001C), Dr. Chun-Ming Tsai (Site 7401: Study D5160C00002), the CRO (b) (4) and the study sponsor of Study D5160C0001C and Study D5160C00002, data submitted to the Agency in support of NDA 208065, appear reliable and can be used in support of the application.

- **Division of Risk Management:** DRISK and DOP-2 concur at this time a REMS for is not necessary to ensure that the benefits outweigh the risks for the FDA proposed indication. .
- **Other Discipline Consults:** None
- **Other Outstanding Regulatory Issues:** None

12. Labeling

- **Proprietary name:** OSE/DMEPA concluded that the proposed proprietary name TAGRISSO is acceptable.
- **OSE/ Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

- **Patient Labeling Team:** The patient labeling team participated in labeling discussions.
- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.
- **Clinical labeling summary:**
 - Indications: remove [REDACTED] (b) (4) was not adequately studied.
 - Dosage and administration: Separate section on preparation for an extemporaneous aqueous dispersion for patients who have difficulty swallowing tablets.
 - Warnings and Precautions: There was vigorous internal debate on whether to include QTc prolongation in this section. Ultimately, upon discussion with QT-IRT, it was decided that given that there was a >15 ms change of QTcF (point estimate 16.2 ms, 90% CI upper bound 17.6 ms), it was appropriate for QT prolongation to remain in Warnings and Precautions. With respect to ILD, the information [REDACTED] (b) (4) was removed [REDACTED] (b) (4) and the 90-day safety update was used to calculate ILD incidence.
 - Adverse Reactions: amended to include updated exposure and safety data from the 90-day safety update. Also revised to more closely comply with the FDA's Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products- Content and Format.
 - Geriatric Use: described exploratory analyses suggesting potential increased adverse reactions in patients 65 years or older as compared to patients younger than 65 years.
 - Clinical Studies: Removed the pooled ORR data from Study 1 and Study 2. Shortened the description of the 32 patients in the dose escalation cohort to focus on the median duration of response.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval
- Risk Benefit Assessment

Patients with EGFR-mutation positive metastatic NSCLC who have progressed on an EGFR TKI and whose tumors harbor EGFR T790M resistance mutations have a serious and life-threatening illness, with an overall poor prognosis and limited effective therapies. The efficacy and safety results in AURA extension and AURA2 demonstrate a favorable benefit-risk profile for osimertinib for patients with EGFR-mutation positive mNSCLC who harbor T790M and have progressed on an EGFR TKI. All review team members recommend approval.

The basis of the approval recommendation is the demonstration of a large magnitude of ORR, 57% (50, 64) in AURA extension, 61% (54, 68) in AURA2. Furthermore, responses appear to be durable, as evidenced by the median duration of response of 12 months in the 32 of 63 patients who responded in the AURA phase 1 cohort. A large magnitude of effect on ORR of suitable duration is a surrogate endpoint that is reasonably likely to predict clinical benefit. Response rate of large magnitude and long duration have been observed in trials with other TKIs targeting specific genetic aberrations (such as EGFR kinase domain mutations and ALK-rearrangements) in mNSCLC, which have subsequently in randomized confirmatory trials demonstrated improvements in PFS of large magnitude when compared to chemotherapy. In an FDA meta-analysis of mNSCLC trials submitted to FDA in the past 10 years, ORR appeared to be strongly associated with PFS (Blumenthal et al, JCO 2015).

Section 21 CFR 314.510 addresses approval based on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the Applicant study the drug further to confirm clinical benefit. As a condition of accelerated approval, the Applicant is required to perform a randomized, multicenter post marketing study or studies to confirm the superiority of osimertinib over standard therapy in EGFR mutation-positive metastatic NSCLC. (b) (4)

(b) (4) given the limited knowledge of the natural history of T790M mNSCLC, FDA requested that a randomized controlled study be submitted as the confirmatory study. FDA did encourage the Applicant to submit (b) (4) results of AURA3, so that the Agency can better assess the performance characteristics (b) (4) as a confirmatory study going forward.

The risks of osimertinib are acceptable relative to the benefits. The Applicant was successful in its phase 1 program of finding an acceptable phase 2 dose, with fewer dose reductions, interruptions, and discontinuations than is typical of other TKIs. The main risks, as highlighted in 'Warnings and Precautions' include rare cases of interstitial lung disease and QT interval prolongation. The common EGFR adverse reactions of diarrhea and skin rash appear to occur less frequently than other TKIs in this pharmacologic class. Ultimately, longer duration of follow-up and randomized controlled trials will further characterize the toxicity profile of osimertinib.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)

The Applicant did not propose a REMS and the review teams did not identify the need for a REMS to ensure the safe use of osimertinib in the indicated patient population.

- Recommendation for Postmarketing Requirements

I agree with the postmarketing requirements proposed by the review teams and agreed upon with the Applicant. Please note that some of the milestone dates may be modified with finalization of the action letter.

Clinical Pharmacology PMRs under 505(o)

1. (b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inhibitor) on the Pharmacokinetics of (b) (4) of osimertinib (b) (4)
2. (b) (4) to Assess the Effect of (b) (4) (a CYP3A4 Inducer) on the Pharmacokinetics of osimertinib (b) (4)
3. (b) (4) to Assess the Effect of (b) (4) osimertinib on the Pharmacokinetics of (b) (4) CYP3A4 Substrate) (b) (4)
4. (b) (4) to Assess the Effect of (b) (4) osimertinib on the Pharmacokinetics of (b) (4) BCRP Substrate (b) (4)
5. (b) (4)

Accelerated Approval PMR under Subpart H

6. Phase 3, Open Label, Randomized Study of osimertinib versus Platinum- Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and (b) (4) (AURA 3)

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/s/

GIDEON M BLUMENTHAL
10/20/2015